



Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy should be selected based upon patient-specific factors: glycemic management needs, cardiorenal risks, comorbidities, cost and access.

Consider **combination pharmacotherapy** at initiation if A1C $\geq 1.5\%$ above target goal.



Consider **early insulin initiation** with extreme hyperglycemia:

- BG ≥ 300 mg/dL
- A1C $> 10\%$
- Signs of catabolism



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Reassess and modify treatment every **3-6 months**



Established/High-Risk of ASCVD, Heart Failure, or Chronic Kidney Disease?

No



Recommended independent of baseline A1C, target A1C goal, or metformin use



ASCVD
(established or high risk)

GLP-1 RA or SGLT2i
with proven CVD benefit



If A1C above target

- On GLP-1 RA? Consider incorporating SGLT2i with CVD benefit (and vice versa)
- Consider low dose TZD (avoid in patients with HF)

Heart Failure
(preserved or reduced EF)

SGLT2i
with HF benefit
- Avoid TZDs
- Avoid saxagliptin



If A1C above target

Chronic Kidney Disease
(eGFR < 60 mL/min and/or UACR ≥ 30 mg/g)

On maximally tolerated **ACEi/ARB**



SGLT2i with primary evidence for reducing CKD progression

- May be initiated with an eGFR as low as 20 mL/min
- Strongest evidence of benefit when UACR ≥ 200 mg/g
- If SGLT2i therapy is contraindicated or not tolerated, use of a **GLP-1 RA** with CVD benefit is recommended



If A1C above target

On SGLT2i? Consider incorporating GLP-1 RA (and vice versa)

CLASS

ASCVD

HEART FAILURE

RENAL

SGLT2is

FDA approved CVD benefit:

- dapagliflozin
- empagliflozin

Neutral:

- dapagliflozin
- ertugliflozin

FDA approved HF benefit:

- dapagliflozin
- empagliflozin

Evidence for benefit:

- canagliflozin
- ertugliflozin

FDA approved renal benefit:

- canagliflozin (DKD)
- dapagliflozin (CKD)

Evidence for benefit:

- empagliflozin

GLP-1 RAs & GLP-1/GIP RAs

GLP-1/GIP RA tirzepatide is under investigation for CV

FDA approved CVD benefit:

- dulaglutide
- liraglutide
- semaglutide (SUBQ)

Neutral:

- exenatide ER
- lixisenatide
- semaglutide (oral)

Neutral

Evidence for renal benefit:

- dulaglutide
- liraglutide
- semaglutide (SUBQ)

NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 12/2022.

Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm

Page 1

References: American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023. Individual manufacturer product labels.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high to very high** glucose-lowering and weight-loss efficacy.



Glucose-Lowering Efficacy

Very High:

Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination therapy

High:

GLP-1 RA (not listed above)
Metformin
SGLT2i
Sulfonylurea
TZD

Intermediate:

DPP-4i



Weight-Loss Efficacy

Very High:

Semaglutide
Tirzepatide

High:

Dulaglutide
Liraglutide

Intermediate:

GLP-1 RA (not listed above)
SGLT2i

Intermediate:

DPP-4i
Metformin



Cost and Access

Add oral options available in generic form/lower cost:

- SU
- TZD*

Consider insulins that are available at lower cost:

- NPH
- Regular

Patient assistance programs may be available for certain brand name medications

*Pioglitazone is available as generic; rosiglitazone is brand only (Avandia)



If A1C above target

Add additional agents based on patient-specific factors including: comorbidities, risks, glycemic management needs, convenience, cost and access

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GLP-1/GIP RA)



Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm



Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy
Consider **early insulin initiation** with extreme hyperglycemia: BG ≥ 300 mg/dL, or A1C $>10\%$ or signs of catabolism present

→ See Page 1 regarding non-insulin initial pharmacotherapy use and selection

References:

American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023., Individual manufacturer product labels.



Reassess and modify treatment every **3-6 months** to avoid therapeutic inertia



Injectable therapy needed to lower A1C?



Consider **GLP-1 RA** or **GLP-1/GIP RA** in most patients prior to insulin
Titrate to **maintenance dose**

Already on **GLP-1 RA** or **GLP-1/GIP RA**?
GLP-1 RA or GLP-1/GIP RA **not appropriate**?
Or is **insulin preferred**?



Assess basal insulin dose adequacy & evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:

- basal dose >0.5 units/kg
- $\uparrow$ bedtime-morning/post-preprandial differential
- hypoglycemia (aware or not)
- high variability



Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors (e.g. cost)

START: 10 units/day or 0.1-0.2 units/kg/day

TITRATE to fasting plasma glucose (FPG) target:

- Follow an evidence-based titration algorithm, e.g. $\uparrow$ 2 units every 3 days until FPG target
- Hypoglycemia is never acceptable; titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, $\downarrow$ dose 10-20%



If A1C is above target



On bedtime NPH? Consider conversion to BID NPH

One possible approach:

START:

- Total dose = 80% of current
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION: Titrate based on the individual's needs



If A1C is above target

Add prandial insulin

Usually start with one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

START:

- 4 units/day or 10% of basal insulin dose
- If A1C $<8\%$, consider $\downarrow$ basal dose by 4 units/day or by 10% of basal dose

TITRATION:

- $\uparrow$ dose 1-2 units or 10-15% twice weekly
- If hypoglycemia occurs for no clear reason, $\downarrow$ dose by 10-20%



If A1C is above target



Consider BID premix insulin

START:

- Usually unit per unit at the same total insulin dose, but may require adjustment for the individual's needs

TITRATION: Titrate based on the individual's needs



Stepwise additional prandial injections

(i.e. 1 then 2 then 3 injections)



Full basal-bolus regimen

(i.e. prandial insulin w/ meals and basal insulin)



Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

START:

- Total NPH dose = 80% of current NPH
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid insulin to each injection or 10% of reduced NPH dose

TITRATION:

- Titrate components of the regimen based on the individual's needs



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